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NEW TRENDS FOR VACCINE PRODUCTION AND UNIDO PROGRAMME ON INDUSTRIAL PRODUCTION OF BIOLOGICALS

Brief presentation by the UNIDO Secretariat*

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The needs of developing countries for the production of biologicals are recently acquiring great urgency. At present there are worldwide some twenty producers of polio and measles vaccines, thirty manufacturers of BCG, forty laboratories that prepare DPT and close to seventy that produce tetanus toxoid, however only a few companies take part regularly in competitive biddings of UNICEF and PAHO providing vaccines for the Expanded Programme on Immunization (EPI) of WHO. In other words, through the above UN agencies, more than 275 million doses of EPI vaccines produced by a few large manufacturers were supplied in 1984 to approximately one third of 90 million children born in more than 130 developing countries in the world (1,2). In order to achieve the goal of EPI, that is providing immunization services against diphtheria, whooping cough, tetanus, measles, tuberculosis and poliomyelitis for every child by 1990, 5-7 times more vaccines would be required. To meet the above increased demand, the existing capacities of the main suppliers of the EPI would have to be enlarged. However, it must be noted that the biological industry, this small but important part of the pharmaceutical industry has some special characteristics such as that, apart from the uncertaintities of the international competitive bidding, it is a high-risk, low-return venture (3). If creation of new capacities for vaccine production would be required in the biological industry, UNICEF most probably will not be able to keep the present low prices (4).

An obvious alternative solution to assure the continuous supply of EPI vaccines is to undertake production in the developing countries at national, subregional and regional level. Several developing countries like Brazil, Colombia, Cuba and Mexico in Latin-America, India, Indonesia and Pakistan in Asia, Algeria and Egypt in Africa have already started an extensive programme on domestic production of vaccines. This is also reflected by the increased number of requests from developing countries for UNIDO's Technical Assistance in this particular subsector of the pharmaceutical industry. Towards this end UNIDO has decided to launch a programme on industrial production of biologicals (IPB). An Advisory Panel on Preventive Medicine has been established and it is considered essential to provide advice and guidance in this field to UNIDO (5).

The strategy of the IPB programme is based on an industrial approach characterized by the concept of unit process and homogenous culture system. This approach also secures the consistency in the

consecutive production lots by means of a built-in quality assurance. It advocates the required transfer of technology through a long-term support programme to make the recipient enable to adopt and assimilate the technology but also to assist in the promotion of new products.

In line with the conclusions and recommendations given by the Second Consultation on the Pharmaceutical Industry in Issue 4: Biologicals, the UNIDO Advisory Panel on Preventive Medicine, in its first meeting, in 1984 recommended that a study should be prepared on the impact of modern technologies on production during the forthcoming decade of priority vaccines (6,7). This study, the "Model Programme for the Production of Vaccines in Developing Countries" is intended primarily for use by Government officials and directors of institutes, responsible for framing and implementing national vaccination programmes. In addition it can be used as guidance by professional staff members responsible for implementing the programmes. It can also serve as a base for comparison of different technologies applied in other laboratories for production and control of conventional vaccines.

The Model Programme summarizes the experience of a single manufacturer, namely the Rijksinstituut voor Volksgezondheid en Milieuhygiene (National Institute of Public Health and Environmental Hygiene, abbreviated as RIVM), Bilthoven, the Netherlands, in the production and quality control of conventional vaccines. It thus offers only one choice of a number of existing technologies. It is nonetheless a well proven technology considered to be in the forefront in some areas of vaccine production.

Since the era of Pasteur and Koch, the technologies of vaccine production have been developed more in an empiric way than by systematic R&D, thus making even industrial scale production more akin to cookery (8). In many countries it has been consigned to governmental institutes. In fact, with some notable exceptions, pharmaceutical industries have become less interested in making the large investments in improving the production and quality control techniques of vaccines and other biologicals. As a result, insufficient use is often made of scientific developments in the fields of biochemistry and biochemical engineering, immunology, microbiology, virology and animal husbandry. In particular, the manufacturing process is often ill defined and even

obsolete. In some instances this will yield relatively crude products (an example is pertussis vaccine), and in addition there is poor consistency between consecutive production lots. In many cases the production process is still largely manual. This leads to a vicious downward spiral where low technology leads to a lack of intellectual stimulation and research. It should be emphasized that, in spite of the rather limited investments made in the development of conventional vaccines, the Expert Committee on Biological Standardization of WHO has established a number of excellent standards and reference materials, as well as international requirements for vaccines which are widely used. These have certainly guided many countries in the production of vaccines of acceptable quality. In the case of smallpox vaccine, the quality control programmes of WHO have contributed to the world wide eradication of this disease.

In recent years a number of developed countries have introduced a new form of quality control. In addition to using as reference the standards established by WHO for laboratory facilities for the control of vaccines and sera, they have instituted methods in compliance with rules for Good Manufacturing Practice (GMP) that have been formally drawn up in recent years (9,10). These rules include procedures for the qualification of personnel and their on-the-job training, the establishment and maintenance of building facilities and equipment for production, control and formulation, and the necessary control of raw materials.

GMP procedures established for the production of conventional vaccines will be generally applied to the growing field of biotechnology, regardless of whether the end product will be used in human or veterinary medicine, agriculture or in industrial processes.

One of the basic concepts of the Model Programme, the unit process was originally proposed by van Hemert (11). The main vaccines considered in the Model Programme are all made using the same basic system employing a stainless steel bioreactor unit (the Bilthoven Unit) which can be sterilized in situ and controlled for parameters concerned with microbial cell growth (12). These include pH, pO_2, pCO_2; also sampling to determine growth, opacity and titre of the required biological products. The use of the Bilthoven Unit allows the same conditions to be maintained during scale-up and greatly improves the consistency of the process. In the beginning it

could not be used for virus cultivation, which requires as substrate mammalian cells obtained from animal organs (e.g kidneys) or consisting of so-called cell strains or cell lines. The microcarrier system developed subsequently by van Wezel at the RIVM made it possible to grow large quantities of mammalian cells on the surface of plastic-like particles, which could be held in suspension in the Bilthoven Unit (13). Large amounts of virus materials can thus be obtained, while modern purification procedures ensure the effective removal of contaminating substances yielding an end product with acceptable levels of impurities including RNA or DNA.

The use of (semi-)industrial techniques, such as the unit processing for production of conventional vaccines, will no doubt be stimulated by the simultaneous introduction of GMP. In the Model Programme it is shown how relatively small amounts (in term of human doses) of different vaccines can be prepared in consecutive production rounds with the same facilities and personnel, provided the GMP-rules are strictly observed. There appears to be no principal objection, for instance, to using in the more distant future the same building facilities and equipment for the production of tetanus toxin and BCG vaccine.

While originally cell lines were not permitted for the cultivation of virus materials for human use (even if inactivated), there is at present a tendency favouring their acceptance for human vaccine production.

It could be argued that the existence of facilities for the production and quality control of conventional vaccines will contribute to a number of inter-related, social and economic objectives: reduction of dependance on supplies; increase of domestic stocks of technical know-how and human capital in many disciplines used in development of biologicals and creation of employment.

The advantage of the Model Programme is that the industrial approach taken allows its application for the production of vaccines and other biologicals developed by new biotechnological methods (e.g. recombinant deoxyribonucleic acid (rDNA) and cell fusion). The pharmaceutical, chemical and food processing industries, in that order, are most likely to take advantage of advances of the new biotechnology. Other industrial sectors that will also be affected, although not as immediately, are the mining, crude oil recovery and pollution control industries. Since fermentation is an indispensable element of biotechnology's support system, the experience

gained through the eventual implementation of the UNIDO Model Programme could be utilized in nearly all the products of biotechnology.

In past decades some developing countries have on the basis of the existing scientific organization established regular educational programmes at university level, to create a nucleus of scientists. This has enabled them to make further considerable progress in absorbing scientific knowledge. Among those countries there are now several where capable and intelligent young investigators can follow, or themselves take part in the generation of new knowledge. The major scientific research of these centres is at present still concentrated in the developed world and knowledge is acquired there at an increasing rate. On the other hand, in only a few developing countries are the "knowledge community" structured in such a way that new knowledge is not only absorbed in the academic centres, but also that it can be put to practical use for the benefit of the community. UNIDO's IPB programme provides transfer of technology through a long-term technical assistance programme, which intends to motivate the staff of the centres for academic research to turn towards application, and such a way widens the scope of activity of the conventional production units of biologicals.

Although the pharmaceutical industry was the last to adopt traditional fermentation technologicals, it has been the first industrial sector to make widespread use of the genetic engineering technologies such as the rDNA and cell fusion.

The genetic engineering of biological systems for the production of pharmaceuticals and biologicals has two general goals:

1. To increase the yield of a pharmaceuticals produced, such as the genetic improvement of the strain of Penicillium chrysogenum for penicillin production; and,

2. To produce entirely new pharmaceutical or biologicals such as polypeptides and proteins that are otherwise scarce (peptide hormones, enzymes, vaccines, antibodies, plasma proteins, interferons,etc.)

Some of the important biologicals already produced or to be produced in the near future are as follows:

1. Vaccines: Hepatitis B vaccine
   Herpes simplex vaccine
   Foot and mouth disease vaccine (FMDV)
   Cholera vaccine

2. Hormones: Insulin
   Growth hormone
   Atriopeptin
   Growth hormone releasing factor
   Beta-endorphin

3. Lymphokines: Interferon, alpha
   beta
   gamma
   Interleukin - 2 (IL-2)
   Tumor necrosis factor (TNF)

4. Enzymes: Tissue Plasminogen activator (TPA)
   Urokinase

5. Coagulation proteins : Factor VIII

6. Human plasma proteins: Albumin

7. Other proteins: Protein A

8. Monoclonal antibodies: For cancer treatment
   For cancer diagnosis
   Antitoxin

If application of rDNA technology becomes a real alternative for large-scale production of plasma proteins, the costs are likely to come from purifying the proteins rather than from producing them. For plasma products such as albumin, approximately 300 tons will have to be manufactured and purified. For products such as Factor VIII, such large amounts will not be required, but purification techniques that will not inactivate this highly unstable enzyme will have to be developed. The world market for both proteins prepared by rDNA technology has been estimated to be as high as US$ 2 billion (14).

Recently rapid and significant progress has been made in the development of vaccines against leprosy and malaria. Hence, there are over 10 million leprosy patients in the world, while more than 350 million people are living in areas, mostly in Africa, where malaria is still highly endemic and where no specific antimalaria measures are being applied, the R&D of vaccines and immunotherapy has great importance (15).

The exciting area of new biotechnology offers almost countless possibilities for R&D of future vaccines. Most probably the vaccines used in the year 2000 will be entirely different from the conventional vaccines administered today. Some of the presently used vaccines are deficient in one or more properties. Specific R&D approaches for new biotechnology vaccines include:

1. New and improved methods for polypeptide synthesis : Synthetic vaccines.

2. Antigens expressed by rDNA in prokaryotic (E. coli) or eukaryotic cells (yeast or mammalian cells) : Purified antigens and subunit vaccines.

3. Modification of microbial genomes for the production of stable, safe, attenuated mutants : Live vaccines.

4. Controlled antigen expression in suitable vector organisms : Recombinant vaccinia viruses for vaccine antigens.

5. New ways of antigen presentation : Antiidiotype vaccines.

6. Carrier proteins for peptide antigens : Antifertility vaccine.

7. Augmentation of protective immune responses : Immunological adjuvants and immunomodulators.

It was almost 200 years from Jenner's discovery of smallpox vaccine to the eradication of this disease in 1977. It is a considerable period of time, which might hopefully be significantly reduced in the case of other

vaccines such as polio or measles. Based on the experiences gained in WHO'global eradication programme of smallpox, a combined approach of improving quality of vaccines, transfer of technology and improving the delivery system might bring the earliest success. Through its IPB programme, UNIDO wish to play the role of catalyst for the transfer of technology between holders and recipients, and with all its competence is ready to assist developing countries in assimilating new technologies and achieving a viable production of standard quality products.

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REPORT*

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PREFACE

Dr. Charles Mérieux, Chairman of the Advisory Panel on Preventive Medicine called on Mr. Domingo L. Siazon Jr., Director-General of UNIDO on 26 September 1985, and presented the UNIDO programme on Industrial Production of Biologicals (IPB) and reviewed the activity of the Panel.

Dr. Mérieux advised the Director-General that the Third Meeting of the Panel held in Bilthoven, The Netherlands on 6-7 June 1985, cleared the Model Programme for the Production of Vaccines and recommended to put forward by UNIDO to the Governments of developing countries. He said that the Panel welcomed the account presented by UNIDO for the implementation of the Model Programme in Africa as a pilot demonstration plant for vaccine production at Garoua, Cameroon (UNIDO/IO.624, paras 10 to 13). Hence the IPB programme was progressing well and expanding fast, he stressed the importance of the continuation of work of the Panel.

The Advisory Panel on Preventive Medicine met in Ottawa, Canada from 11 to 12 March 1986 in order to review the progress of UNIDO's IPB programme in accordance with the recommendations of its third meeting (UNIDO/IO.624, paras. 8 to 21) and to discuss the preparatory work carried out by UNIDO to the Third Consultation on the Pharmaceutical Industry to be held in Spain in 1987.

I. ORGANIZATION OF THE MEETING

Opening of the Meeting

1. The meeting was opened by Dr. Charles Mérieux, Chairman of the Panel. In his inaugural address on behalf of the Panel he expressed his acknowledgements to Dr. Maurice Brossard, Vice-President Biotechnology, National Research Council Canada, Ottawa for hosting the meeting. He also expressed his appreciation to the members of the Panel for their genuine and constructive attitude in their former meetings, that made his duty to chair this particular committee as a honour.

The Unido Secretariat's Presentation to the Advisory Panel

2. Mrs. A. Tcheknavorian, Head of the Chemical Industries Branch, Division of Industrial Operations, Secretary of the Advisory Panel greeted the members of the Panel, the observers of the Government of Canada and the representatives of WHO, PAHO and UNICEF.

She advised that the preparation of the "Model Programme for the Production of Vaccines in Developing Countries" has progressed well and it is close to be completed. She requested the Panel to agree that Dr. M. Philippe drafts an explanatory memorandum to the Model Programme as recommended by the Third Meeting of the Panel (UNIDO/IO.624, para 12).

In her presentation she gave a brief account of the programme for the Industrial Development Decade for Africa (IDDA), 1980 - 1990. The General Assembly decided in its resolution 39/233 to allocate at least US$ 5 million, on a permanent annual basis, from the regular budget of the United Nations in order to enable UNIDO to assist African countries and the intergovernmental organizations concerned in the implementation of the IDDA programme. With regard to the Model Programme and the "Regional Meeting on Availability and Distribution of Vaccines Produced in Africa", US/RAF/84/252, she noted UNIDO must not either raise vain hopes or provoke decisions that might lead to the failure of projects. In the project development and implementation at least three parties, namely

(i) the executive agency and/or investor, (ii) the organization responsible for quality control, e.g. Ministry of Health, WHO and (iii) the technology holder providing the transfer of technology (TOT) should co-operate. She highlighted the importance of the proper utilization of donations. Donations should not either be misused or demotivate the acceptor. She emphasized that a capability should be created in Africa leading stage by stage towards a self-reliance, however the reality of establishment of new units for vaccine production should carefully be investigated.

If a technical and at a later stage technological capability could be developed for production of conventional vaccines in Africa, it might open the door for the development of biotechnology, in other words through its IPB programme UNIDO is creating the infrastructure to enable African countries to absorb biotechnological methods.

3. Mrs. Tcheknavorian also stressed the global nature of the IPB programme. She recalled the first attempts in co-operation between Connaught Laboratories Limited, Willowdale, Ontario, Canada and UNIDO years ago that led to a mutual understanding and information exchanges. The characteristics of the IPB programme are very similar to those of the Connaught Technology Transfer Plan and therefore a joint endeavour to develop projects for production of conventional vaccines in developing countries is foreseen.

4. She finally briefed the Panel on Dr. Assaad's visit to UNIDO on 7 February 1986 and on the visit of Mr. G. Latortue, Head, Negotiation, Department, UNIDO to WHO on 10 February 1986. In these visits joint UNIDO/WHO activities for the Third Consultation on the Pharmaceutical Industry to be held in Spain in 1987 was agreed.

<u>The Agenda of the Meeting</u>

5. The agenda was as follows:

(i) Opening of the meeting

(ii) Adoption of the Agenda of the Meeting

(iii) Adoption of the Report on the Third Meeting of the Advisory Panel on Preventive Medicine, Bilthoven, The Netherlands, 6-7 June 1985, UNIDO/IO.624

(iv) Adoption of the "Model Programme for the Production of Vaccines in Developing Countries ", UC/GLO/84/120

(v) Discussions on "Manufacturing and Quality Control of freeze-dried BCG vaccine prepared from surface culture " as a part of the Model Programme, UC/GLO/84/120

(vi) Discussions on preparation of an explanatory memorandum for the Model Programme

(vii) Adoption of project document for the Regional Meeting on Availability and Distribution of Vaccines Produced in Africa, US/RAF/84/252

(viii) Discussions on the implementation of the Model Programme in Africa

a) Establishment of a Pilot Demonstration Plant for Production of Vaccines for Africa in Cameroon, RP/CMR/85/601

b) Rehabilitation of BCG production laboratory in Madagascar, SI/MAG/84/801

(ix) Discussions on the new trends in vaccine production and UNIDO programme on Industrial Production of Biologicals

(x) Discussions on the possibilities of fund raising for the IPB programme

(xi) Identification and clearance of new issues for the Third Consultation on the Pharmaceutical to be held in Spain, March 1987

(xii) Other proposals on the subject of Third Consultation deemed essential by the Advisory Panel

(xiii) Date of the next meeting

(xiv) Closing of the meeting

Adoption of Documents of the IPB Programme

6. During the meeting the Panel approved the Report of the Third Meeting (UNIDO/IO.624), the "Model Programme for the Production of Vaccines in Developing Countries", UC/GLO/84/120 and the project document for the "Regional Meeting on Availability and Distribution of Vaccines Produced in Africa", US/RAF/84/252.

Documentation

7. Working papers for the meeting were as follows:

(i) Model Programme for the Production of Vaccines in Developing Countries, UC/GLO/84/120;

(ii) Manufacturing and Quality Control of Freeze-dried BCG Vaccine Prepared from Surface Culture, Technical Report UC/GLO/84/120;

(iii) Regional Meeting on Availability and Distribution of Vaccines Produced in Africa, US/RAF/84/252;

(iv) Establishment of a Pilot Demonstration Plant for Production of Vaccines for Africa in Cameroon, RP/CMR/85/601 (by Dr. A. L. van Wezel);

(v) Renovation du Laboratoire de Production de BCG, Phase I, SI/MAG/84/801 (by Dr. L. Lugosi); and

(vi) New trends in vaccine production and UNIDO programme on Industrial Production of Biologicals, UNIDO Secretariat.

8. An Explanatory Memorandum for the Model Programme was prepared, distributed and discussed in the meeting. This document will accompany the Model Programme (Annex I).

Visits

9. The representatives of Connaught Laboratories Limited and the Canadian Government expressed their interest to develop a transfer of technology programme for production of biologicals jointly with UNIDO through its IPB programme. To demonstrate their technology transfer programme the Connaught Laboratories Limited (CLL), Willowdale, Ontario, Canada invited the members of the Panel to attend a Seminar on the subject. The Seminar was held on 10 March 1986. The members of the Panel were welcomed to CLL by Mr. A. Davies, President. In the morning an introduction to CLL operations, namely production of viral and bacterial vaccines, diagnostics and plasma fractionation was presented by Mr. P.J. Campbell, Vice-President, Operations. the Connaught Technology Transfer Plan was presented by Mr. C. Cossette, Vice-President, Marketing and Mr. R. E.Binnerts. Finally a lecture on potential funding of technology transfer projects by aid agencies was

delivered by Mr. J. Kieran. In the afternoon the members of the Panel visited the CLL facilities. A general discussion closed the visit.

A brief outline of the Connaught Technology Transfer Plan is given in Annex II.

It was decided that a high level delegation of Connaught will visit UNIDO Headquarters in order to discuss the co-operation programme in the field of biologicals production in developing countries. This co-operation would be very important hence it would offer the UNIDO IPB programme an alternative technology package for vaccine production, in addition to the technology of the Rijksinstituut voor Volksgezondheid en Milieuhygiene (RIVM).

II. CONCLUSION AND RECOMMENDATIONS

10. The report of the Third Meeting of the Panel was adopted with slight modifications (UNIDO/IO.624).

11. After a lengthy discussion the Panel adopted the Model Programme for the Production of Vaccines in Developing Countries without any substantial changes. The Model Programme based on the experience of the Rijksinstituut voor Volksgezondheid en Milieuhygiene (RIVM) gives technological and economic details on production of seven vaccines, namely BCG, diphtheria, tetanus, pertussis, inactivated poliomyelitis, measles and rabies vaccines. It offers a technology package for production of vaccines against the six target diseases of the EPI of WHO and the tissue culture rabies vaccine. It should be noted that this technology package is only one option among a number of technologies, nevertheless it is considered to be in the fore-front of some areas of vaccine production. An explanatory memorandum has been written to the Model Programme with the list of Panel members (Annex 1).

12. The Panel recommended that a series of documents be prepared including:
    - transfer of technology for biological production;
    - production of BCG vaccine (surface cultivation);
    - production of oral poliomyelitis vaccine (Sabin);
    - directory of potential partners for transfer of technology for biological production.

13. The working paper entitled "Manufacturing and quality control of freeze-dried BCG vaccine prepared from surface culture" UC/GLO/84/120 was discussed and the Panel recommended that it should be updated based on the comments of the members of the Panel.

14. Hence the production of oral polio vaccine is not included in the Model Programme, the Panel recommended that Connaught Laboratories Ltd. and Gerencia General de Biológicos y Reactivos, México prepare this document within the next six months and distribute it before the next meeting of the Panel.

15. The Panel recommended that the Third International Seminar on Immunization in Africa to be held in Niamey, Niger between November 1986 and January 1987 should include a session on industrial aspects of vaccine development in line with the objectives of the project document US/RAF/84/252 - Regional Meeting on Availability and Distribution of Vaccines Produced in Africa (UNIDO/IO.624, para 36). Hence the Third International Seminar on Immunization in Africa co-sponsored and co-organized by the Task Force for Child Survivors (Bellagio group), the Panel recommended that UNIDO takes necessary steps to become a member of the Task Force (UNIDO/IO.624, para 8).

16. The Panel noted that UNIDO is in close collaboration with the Dutch Government, with Fondation Mérieux and RIVM in the project on the Establishment of a Pilot Demonstration Plant for Production of Vaccines for Africa in Cameroon, RP/CMR/85/601 and WHO will collaborate in the quality control aspects of the project. It was agreed that a status report on the project in Cameroon be presented in the next Panel meeting.

17. The Panel recommended that all its documentation be presented at the Third Consultation on the Pharmaceutical Industry to be held in Spain in 1987. It was also agreed that WHO presents papers on the Programme for Vaccine Development and on the transfer of technology to developing countries. It was agreed that UNIDO and WHO collaborate in presentation on the issue of biological production and quality control.

18. The Panel noted the suggestion of PAHO's representative on preparation a document on diagnostics (UNIDO/IO.624, para 19) and recommended that PAHO takes the lead in the subject and reports on this issue.

19. The Panel recommended that representatives of FAO, UNDP and World Bank be invited for its fifth meeting.

20. The Panel recommended that Mr. Robbert E. Binnerts be invited as permanent observer for its forthcoming meetings.

21. The Panel recommends that its fifth meeting takes place before the Third Consultation on the Pharmaceutical Industry and be held in Macao at the end of 1986.

III. SUMMARY OF THE DISCUSSIONS

22. The report on the Third Meeting of the Panel was adopted with minor corrections. The corrections are as follows:

- In Preface, in para 1, line 1 and para 3, line 3: meeting should read meetings;
- In I.2, line 4: meting should read meeting;
  line 15: was should be replaced by were;
- In II.11, line 4: methods should read method;
  15, line 2: was should be replaced by were;
- In III.22, line 11: includes should read include;
  line 16: participating should read participating in;
  25, line 1: in length should read at length;
  line 2: the word to should be deleted;
  line 4: point should read points;
  line 8: the UNIDO's should read that UNIDO's;
  26, line 2: omiting should read omitting;
  27, line 2: stationery should read stationary;
  30, line 3: reserach should read research;
  32, line 3: the word dose should be deleted;
  33, line 7: the word enough should be deleted;
  35, line 15: strenghtening should read strengthening;
  37, line 2: in should be replaced by at;
  40, line 6: jointly should read joint;
  line 7: invitation should be replaced by immunization.

23. The Panel reviewed and discussed the final draft of the Model Programme for the Production of Vaccines in Developing Countries, UC/GLO/84/120. The Panel noted that the document was commented and edited by Dr. A.J. Beale, Wellcome Biotechnology Ltd., Beckenham, Kent, UK and agreed that his name be listed as one of the authors.

Several members emphasized that the technologies given in the Model Programme are only one of the possible choices of technology (UNIDO/IO.624, para 12). Referring to the discussions of the Third Meeting of the Panel (UNIDO/IO.624, para 28) several members stressed

the advantage of a multipurpose facility using the principle of unit processing for the production of conventional vaccines.

24. A representative of WHO stated that unit processing has not been considered by WHO. He said that unit processing can be used in special circumstances if there are appropriate safeguards to assure the potency and safety of the products. The quality control department could be located in the same physical set up as the production. He stressed that the development of an independent national quality control authority should be made stage-wise. At the first stage the administrative separation of the national quality control authority can be carried out. He also noted that the GMP requirements of WHO is 20 years old, and suggested that if they are revised, they should take into account the recent technical advances achieved in certain industrialized countries.

25. The Panel agreed that instead of suggesting application possibilities for the principle of unit processing, a few examples are given for what the concept of unit processing does not mean . Unit processing does not mean that physically the same bioreactor unit is used for production of bacterial and viral vaccines. Furthermore, the Panel would, never for example suggest that physically the same bioreactor unit should be used for production of BCG and tetanus vaccines.

26. Several members of the Panel emphasized that there are a number of alternative production systems and methods for the manufacture of conventional vaccines and therefore they recommended to expand the Model Programme. One of these widely used alternative methods is the production of oral poliomyelitis vaccine. It was agreed that the Connaught Laboratories and the Gerencia General de Biólogicos y Reactivos, México prepare a document on oral polio vaccine. The document should cover aspects of production, quality control, accounting, facilities and training, that is the outline of the Model Programme. It was further agreed that in the first part of the document Connaught gives detailes on human diploid cell vaccine and in the second part the Mexican manufacturer

prepares the method of primary monkey kidney cells. The paper on oral polio vaccine will be prepared within the next six months and discussed in the fifth Panel Meeting.

27. The Panel discussed in depth the working paper UC/GLO/84/120 entitled "Manufacture and quality control of freeze-dried BCG vaccine prepared from surface culture". It was agreed that the first draft of the document clearly follows the principles based on which the Model Programme has been prepared. Several members of the panel emphasized the usefulness of production and quality control protocols that are given as illustration, however it was agreed that the description part of the document should be more detailed. The next draft taking the comments of the Panel members into account will be prepared for the next meeting.

28. Dr. Philippe, a member of the Panel was requested by the Secretary of the Panel to prepare an explanatory memorandum, that will be a preamble of the Model Programme (Annex 1). The explanatory memorandum has been prepared with the list of Panel members as it was recommended in the Third Meeting of the Panel (UNIDO/IO.624, para 12).

29. After a thorough discussion the Panel agreed that the documents on polio and BCG vaccines should be published as a series of additional documents to the Model Programme. Further documents will include transfer of technology for production of biologicals and list of technology holders providing technology transfer for biological production.

30. The project document US/RAF/84/252 - Regional Meeting on Availability and distribution of Vaccines Produced in Africa was discussed in depth. A representative of WHO noted that the WHO Regional Office for Africa (AFRO), Brazzaville does not cover all Africa. The representative of PAHO stressed that donations of UNICEF and other agencies should be regarded as relief in emergency situation. He emphasized that a solid infrastructure should be created at regional level. He mentioned that the development of a Latin American "common market" for biologicals was already suggested by PAHO in 1964. Similarly to the PAHO center for foot and mouth disease vaccine in Brazil he suggested the establishment of an African regional center for veterinary vaccines.

31. The Panel also touched upon the subject of vaccine donation in the Expanded Programme on Immunization of WHO. The donation of vaccines may be considered by the responsible authorities of many developing countries as a permanent solution for supply to their national immunization programmes. If free donation could be regarded as a final long-term solution for supply of vaccines, local production will never be feasible for the recipient countries since the costs of donation is zero. UNIDO Secretariat brought up the subject that it would be vitally important that UNICEF makes a clear statement on its donation programme with regard to its size and duration, and the conditions required for participating as recipient in the programme. Such a statement would have essential importance not only for the responsible authorities of developing countries planning and implementing national immunization programmes but for the biological industry.

32. A member of the Panel stated that cost-benefit can easily be calculated in case of veterinary vaccines, however those calculations with human vaccines are always arbitrary since the death of a child cannot be expressed with any financial terms.

33. Another member said that the basic tendency of the history of mankind is the transfer of knowledge. He felt that if capability in biotechnology can not be created in Africa, the Sahelian and Subsaharan famine cannot be overcome in the long run.

34. A member suggested that the UNIDO Regional Meeting on the Availability and Distribution of Vaccines Produced in Africa could be held together with the Third International Seminar on Immunization in Africa, (UNIDO/IO.624, para 36). He advised the Panel that 1986 is the Year of Immunization in Subsaharan Africa for the 46 member countries of the WHO Regional office in Brazzaville. The Third International Seminar will be held between November 1986 and January 1987. The exact date of the Seminar will be communicated to the Panel members in due course. He mentioned that the first and second seminars were held in Bamako and Dakar in 1974 and 1981, respectively. Hence there is a lot to be done to promote the Expanded Programme on Immunization in Africa, the Task Force for Child Survival (Bellagio group) including WHO, UNICEF, UNDP, World Bank and Rockefeller Foundation decided

to co-sponsor and co-organize this Seminar. He felt that to hold the UNIDO Regional Meeting together with the Third International Seminar would be rather complicated but also very advantageous. He suggested to hold the UNIDO meeting immediately after the Seminar since by that way the participants could profit from the first meeting. The programme of the UNIDO meeting should be carefully studied hence the Third International Seminar is a technical meeting while the UNIDO meeting seems to be a political one. Finally he suggested to change the order of the immediate objectives of the project document, such a way that objective (iii) replaces (i) and objective (i) replaces (iii). Objective (ii) remains unchanged.

35. After a long discussion the Panel accepted that the UNIDO Regional Meeting on the Availability and Distribution of vaccines in Africa, US/RAF/84/252 should be held together the Third International Seminar on Immunization in Africa. The Panel unanimously agreed with the Secretary's arguments that production and quality control of vaccines and the immunization, that is the use of vaccines should be discussed together, hence the governments of Subsaharan African countries should realize the interaction between them. She also stated that UNIDO organizes a technical meeting, however it should not be considered as a UNIDO meeting. All interested parties from Governments of African countries and multilateral and bilateral agencies should be invited. Based on the conclusions and recommendations of this technical meeting a UNIDO policy meeting will be organized as a second meeting on the subject in due course.

36. The UNIDO Secretariat presented to the Panel the report of Dr. van Wezel on the project RP/CMR/85/601 - Establishment of a Pilot Demonstration Plant for Production of Vaccines for Africa in Cameroon. Hence the Government of Cameroon requested through UNIDO a four year initial support programme after the execution of the project, the fielding of a second mission, the mission of Dr. van Wezel was requested by the Dutch Government. The project will be executed by a subcontract with RIVM, Bilthoven, The Netherlands. The preparation of the detailed substantive terms of reference for the subcontract with the list of equipment being provided are in progress.

37. The Secretary of the Panel specifically requested the representatives of WHO to collaborate in setting up of a quality control laboratory for vaccines in Cameroon. WHO welcomes such collaboration. However, WHO has to be asked by the Government, otherwise there is no entry point.

38. The UNIDO Secretariat presented to the Panel the report on project SI/HAG/84/801 - Renovation du Laboratoire de Production de BCG, Phase I. This small scale technical assistance project provided expertise and training in production and quality control of BCG vaccine and the revision of the freeze-drier, that is the major equipment of production with the necessary spare parts. It was noted that UNIDO and UNICEF co-ordinate their activities in this project. Through this report as a case report the necessity of co-ordination of the activities of the different UN agencies was discussed.

39. The UNIDO Secretariat presented to the Panel a paper entitled "New Trends in Vaccine Production and UNIDO Programme on Industrial Production of Biologicals". The advantage of the Model Programme that its industrial approach makes it enable to use for production of vaccines and other biologicals developed by new biotechnological methods characterized by genetic engineering of recombinant deoxyribonucleic acid (rDNA) and cell fusion. Through its IPB programme, UNIDO wish to play the role of catalysator between technology holders and recipients, and is ready to assist developing countries in assimilating new technologies and achieving a viable production of standard quality products.

40. A member stressed that any programme in new biotechnology should start with training of personnel in second generation of vaccines. He recalled that because of the complexity of this field, new policy is being developed by WHO. He advocated the development of a joint WHO/UNIDO policy with regard to the industrial aspects of production of new biotechnology products.

41. Another members felt that if the second generation of vaccines will be produced widely in industrialized countries, the present situation with regard to the availability of conventional vaccines in many developing countries might become worse. Therefore transfer of technology for at least those developing countries possessing the necessary infrastructure should be promoted in the field of production of conventional vaccines.

42. The Panel noted that UNIDO is looking for funds for the IPB programme and contacts have been made with the Governments of Canada, France and the Netherlands.

43. The items for the agenda of forthcoming Panel meetings were discussed in depth with particular reference to the UNIDO Third Consultation on the Pharmaceutical Industry to be held in Spain in 1987. A member of the Panel and the representative of PAHO suggested a joint PAHO/UNIDO meeting in Latin America on diagnostics. It was agreed that PAHO takes the lead in the programme on diagnostics, and the representative of PAHO will present the programme in one of the next Panel meetings. Several members suggested that a TOT programme for production of diagnostics should be implemented through TCDC.

44. A member proposed that UNIDO presents the reports on the UNIDO Seminars on Blood Derivatives as well as a progress report on the Cameroon project.

45. Another member suggested that UNICEF should present a report on its activity in the field of biological production.

46. The representative of UNICEF noted that UNDP and World Bank have also developed projects on biological production and he suggested to invite representatives of those organizations and request them to give reports on their activities in this particular field.

47. The Panel agreed that its fifth meeting will be held in Macao at the end of November 1986.

48. The Panel accepted the Chairman's invitation to hold the sixth meeting in Lyon, France in April 1987 after the Third Consultation on the Pharmaceutical Industry.

49. The Panel accepted its member's invitation to hold the seventh meeting in Mexico. The date of this meeting will be decided later on.

50. A representative of WHO handed over a paper on national production of vaccines in developing countries. This general paper does not give any offer for technology transfer but gives a list of questions to be settled between the recipient and technology holder before making decision on implementing such a project.

Annex I

Explanatory Memorandum

The Model Programme for the Production of Vaccines in Developing Countries is intended primarily for use by government officials and directors of institutes who are responsible for structuring and implementing national immunization programmes. The Model programme may also be of general guidance to the professional staff members in charge of vaccine production. It may, in addition, serve as a basis for comparing different technologies applied in other laboratories for the manufacture and quality control of conventional vaccines.

This report summarises the RIVM's experience in production and control of conventional bacterial and viral vaccines currently used in national immunization programmes in the Netherlands. It therefore offers only one option among a number of technologies. The technology described is nevertheless considered to be in the fore-front of some areas of vaccine production, i.e. the unit-processing principle as proposed by van Hemert.

It must therefore be stressed that this is a Model Programme and that there are alternative production systems and methods. The production of oral poliomyelitis vaccine is not included in the present Programme; it will be covered in a later UNIDO document.

Understandably, a preliminary analysis of the local industrial infrastructure and prevailing economic conditions must be made, and appropriate scientific and technological educational programmes must be devised if the required transfer of technology is to take place successfully. A good organizational and managerial infrastructure with the optimal use of human resources is essential for the success of such undertaking. There are, of course, other aspects of technology transfer over and above the execution of a project plan derived from a sound proposal.

A continuing support services plan may be envisaged at the termination of the execution stage. Such a plan can comprise, on a yearly or two-yearly basis: a GMP audit, spare part procurement, performance of parallel quality

control tests, training of new senior staff, implementation of new WHO requirements and raw material testing. Additional aspects include the guarantee that the supplier shall install the purchased equipment and ensure that all machinery performs according to specifications. Maintenance and training of maintenance personnel are key considerations. A full understanding of the concept of quality assurance is equally important. Last but not least, a long-term funding commitment is indispensable for projects involving the production and control of biological products.

The Model Programme will be followed by a series of UNIDO publications including technical documents on production and quality control of BCG vaccine produced on surface culture and of oral poliomyelitis vaccine, a paper on technology transfer for biological production and a directory of potential partners in transfer of technology for biological production.

The UNIDO Secretariat acknowledges to the following Panel members and the representatives of WHO and UNICEF for their comments and advice during the preparation of the Model Programme:

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Annex II

TECHNOLOGY TRANSFER FOR BIOLOGICAL PRODUCTION

Introduction

For the implementation of their "Expanded Programme on Immunization", Governments may wish to consider undertaking local production of certain biological products. To assist in the rapid establishment of such local production, Connaught Laboratories have formulated a Technology Transfer Plan which already has been implemented successfully in Pakistan. These projects are as follows:

"Intermediate" production of oral polio vaccine;
"Basic" production of measles vaccine; and
Production of human diphoid cell rabies vaccine.

Connaught can offer technology transfer for manufacture of the following products:

Diphtheria Toxoid
Pertussis Vaccine --------and combinations
Tetanus Toxoid
Injectable Poliomyelitis Vaccine (Salk;and combinations)
Oral Polio Vaccine (Sabin)
Measles Vaccine (Live, Attenuated)
Rabies Vaccine (Human Diploid Cell)
Human Plasma Fractions
(e.g. Normal Serum Albumin, Immune Serum Globulin)
Meningococcal Vaccine (A,C, W-135, Y)
Intravenous Infusion Fluids

The Main characteristics of the Connaught Technology Transfer Plan

This plan as devised by Connaught consists of two distinct phases:
"Intermediate" Production (manufacture of ready-for-use preparations from imported bulk components)
"Basic" Production

The implementation of the Technology Transfer Plan comprises four separate stages:

The Project Proposal

The Project Plan

The Execution of the Project Plan

The Continuing Support Services

Details of the Connaught Technology Transfer Plan

The Project Proposal broadly outlines the following topics:

Products and quantities to be produced;

Requirements for manufacturing and quality control, buildings, utilities and equipment;

Production materials;

Personnel;

Connaught's services to be provided;

Approximate costs of the project.

The Project Plan consists of the following:

Design of the physical facilities;

Engineering drawings for air-conditioning/purification and all other services;

Detailed specifications for equipment and production materials and their potential sources;

Personnel training schedules (in-situ and in Canada/USA);

Project schedules, including Connaught's activities;

Detailed costing for total project.

The Execution of the Project will comprise the following services by Connaught:

Supervision of construction of building(s) for production and quality control (Note: In selected instances, arrangements can be made with a process engineering company in Toronto to undertake the erection of the physical facilities and the installation of air conditioning purification and all other services)

Procurement of equipment, etc. (if required);

Training of personnel at Connaught in all aspects of production and quality control;

Provision of Connaught staff to supervise the commissioning of the buildings and equipment, the preparation of the first lots of the products in the new facilities and the quality control thereof;
Performance of parallel quality control tests by Connaught, on each lot of product until each party is functioning properly;
Provision of all necessary manuals and other documentation as well as assistance in the registration of all products with the local regulatory authorities.

The Continuing Support Services Plan

This plan should be prepared at the same time as the project, and should be put into action at the termination of the Execution stage.
It can comprise all or any of the following services on a yearly or two-yearly contractual basis:

GMP Audit
Spare Part Procurement
Procurement of Consumables
Assistance in solving such production and quality control problems as may arise from time to time (trouble shooting service)
Performance of parallel quality control tests
Training of new senior staff
Implementation of new WHO requirements
Raw material testing

Keys to the success of technology transfer

During the execution of the project and the continuing support services particular attention should be paid to the following problems.

Staff of the technology holder should be at the project site along the whole period of construction.

System of professional promotion should be incorporated into the project through training programmes

Training in maintenance of equipment should be organized at project site and in the premises of equipment manufacturers.

Lower level personnel should be trained at project site and operation manuals should be provided in local language.

Equipment should be shipped if possible only by air. The supplier should be responsible for installation and trial runs.

Training in quality assurance, quality control and record keeping should be carried out.

Annex III

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